

REMARKS

Information Disclosure Statement

Applicants file concurrently herewith following references in an Information Disclosure Statement for the Examiner's consideration.

- (1) Hans-Georg RAMMENSEE (hereinafter Rammensee) "Chemistry of Peptides Associated with MHC Class I and Class II Molecules," Current Biology Ltd., Current Opinion in Immunology, 1995, pgs. 85-96
- (2) Thomas M. Devlin, Ph.D. (hereinafter Devlin-1), "Amino Acid Composition of Proteins," Textbook of Biochemistry with Clinical Correlations, 1992, pgs. 27-31
- (3) Thomas M. Devlin, Ph.D. (hereinafter Devlin-2), "DNA: The Replicative Process and Repair," Textbook of Biochemistry with Clinical Correlations, 1992, pgs. 642-643.
- (4) Thomas M. Devlin, Ph.D. (hereinafter Devlin-3), "Restriction Endonucleases and Restriction Maps," Textbook of Biochemistry with Clinical Correlations, 1992, pgs. 769-770.
- (5) Primepares G. Pal, et al. (hereinafter Primepares) "Immunization with Extracellular Proteins of Mycobacterium Tuberculosis Induces Cell-Mediated Immune Responses and Substantial Protective Immunity in a Guinea Pig Model of Pulmonary Tuberculosis," Infection and Immunity, November 1992, pgs. 4781-4792.
- (6) Peter Andersen (hereinafter Andersen), "Effective Vaccination of Mice against Mycobacterium Tuberculosis Infection with a Soluble Mixture of Secreted Mycobacterial Proteins," Infection and Immunity, June 1994, pgs. 2536-2544.

It is requested that the Examiner acknowledge consideration of the same and return a copy of the filed PTO-Form 1449 which has been initialed, signed, and dated by the Examiner.

The rejections of Claims 19 and 25-26 under 35 U.S.C. § 112, first and second paragraph, are respectfully traversed.

In regard to the Office's position concerning the term "a portion" of SEQ ID NO:2 or SEQ ID NO:3, it is stated that, at the date the invention was made, a skilled artisan knew from general technical knowledge, the sizes of protein fragments that are required for inducing an immune response.

For example, Rammensee shows that the peptide length which is necessary for enabling an association of the peptide epitopes to the MHC Class I and Class II molecules is of:

- (i) 9 amino acids residues in length for peptides to be associated with MHC Class I antigens (see page 85); and
- (ii) 12-25 amino acids residues in length for the peptides to be associated with Class II MHC antigens (see page 89, "Peptide Length").

Further, in contrast to the Office's position, the breadth of Claim 19 is not so large as to prevent enablement, since these sequences are peptide fragments from the known amino acid sequences of SEQ ID NO:2 and SEQ ID NO:3. One of ordinary skill can easily obtain by routine techniques every peptide fragment that fall under the scope of Claim 19, for instance by molecular biology techniques as it is expressly specified from page 7, line 24 to page 8 line 1 of the specification.

For instance, one skilled in the art can use restriction enzymes in order to cleave the DNA encoding the protein sequence of SEQ ID NO:2 or SEQ ID NO:3 and then clone the thus excised DNA fragment in a vector already containing a nucleotide sequence encoding the heterologous antigen contained in the hybride protein which is claimed. Notably, restriction enzymes and their use for sub-cloning DNA fragments was widely known at the date the invention was made, these techniques being disclosed, for example, in Devlin-2 and Devlin-3.

In the matter of the term "having secondary differences or limited variations," it is noted that page 5, lines 13-17 of the Specification "proteins having secondary differences or limited variations in their amino acid sequences...do not functionally modify them by comparison with the proteins having the sequences SEQ ID NO:2 and SEQ ID NO:3."

In contrast to Office's position, the various amino acid residues and their physical chemical properties were sufficiently well characterized, at the date of the invention, for having been classified so that the one skilled in the art knows well which amino acid substitution might be effected. So that the substituted amino acid residue possess the same physical chemical properties as that of the corresponding amino acid residue that was initially contained in each of the amino acid sequences of SEQ ID NO:2 and SEQ ID NO:3, such as disclosed in Devlin-1.

Finally, it is noted that the Office has recognized that "it is known that many amino acids substitutions are possible in a given protein" and also that "these regions can tolerate only very little substitutions" (see page 5 of the Office Action dated July 26, 2004).

Concerning the Office's position that the expression "polypeptide comprising an amino acid sequence which is able to induce an immune response in animal" is unclear, is now moot in view of the amendment to Claim 19. For example, amended Claim 19 now specifies "antigenic determinant," rather than "amino acid sequence."

Further, the hybrid polypeptides that are claimed are composed of two antigens, respectively (i) a polypeptide corresponding to a portion of SEQ ID NO:2 or SEQ ID NO:3, and (ii) an heterologous antigenic polypeptide, the general definition of which is expressly specified page 4, line 34 – page 5, line 4 of the specification. The heterologous antigenic polypeptide may comprise, for instance, epitopes from a toxin (diphtheria, or tetanus toxin) or a viral protein (HBS antigen of HBV virus, VP1 antigen of the polyomyelitis virus), such as disclosed on page 5, lines 5-9 of the specification.

In the specification, it is stated that the proteins corresponding to SEQ ID NO:2 or SEQ ID NO:3 induce a strong immune response in human (see page 8 lines 4-7 of the specification). Further, the association of a portion of the proteins of SEQ ID NO:2 or SEQ ID NO:3 originating from *Mycobacterium tuberculosis* with heterologous polypeptide

antigens which induce by themselves a weak immune response, allows to boost the immune response against these heterologous antigen, such as explained on page 8, lines 8-11 of the specification.

These heterologous polypeptide antigens have no carrier or hapten effect. The industrial interest of these hybrid proteins consists of protecting human through a unique immunisation against simultaneously more than one disease, as explained on page 8, lines 26-29 of the specification.

With regard to enablement of the immunization protocols, at the date the invention was made, one of ordinary skill was well aware of various protocols for immunising human against pathological antigens, thus including when using the hybride proteins that are presently claimed as the antigens.

The references of Primepares and Andersen, cited concurrently herewith, disclose successful immunisation protocols using protein antigens originating from *M. tuberculosis* that induce an efficient protection of the immunized animal against an infection by *M. tuberculosis*.

In view of the amendments to the claims and the comments above, it is requested that the Examiner withdraw these two rejections.

The rejection of Claims 19 and 25-26 under 35 U.S.C. § 103(a) over Wieles in view of WO 92/21758, as evidenced by U.S. Patent No. 6,060,259 (hereinafter US '259) is respectfully traversed.

The known homology between the protein disclosed by Wieles and that disclosed by Marchal concerned only N-terminal immunoacid sequences of these two proteins, since only these N-terminal portions of both proteins have been sequenced. Further, the amino acid homology between the N-terminal sequences of these two proteins is only of 47% (see Wieles et al., Abstract, page 255, left column and figure 4).

Thus, Wieles did not disclose nor suggest any technical means which would enable, or even motivate, one of ordinary skill to isolate and characterize, the proteins of sequences SEQ ID NO:2 or SEQ ID NO:3. A fortiori, one of ordinary skill would have found no indication in Wieles as to design and/or manufacture the hybride protein which is presently claimed.

Further, the protein disclosed in Wieles consists of a protein originating from *Mycobacterium leprae*, whereas the protein disclosed in US '259 originates from *Mycobacterium bovis* BCG. Consequently, following the Office's reasoning, one of ordinary skill would arrive at hybrid proteins usable for inducing an immune response against an antigen from *Mycobacterium leprae*, but would not have obtained a protective immune response against tuberculosis which is the goal according to the present invention.

In view of these facts, it is respectfully requested that the Examiner withdraw this rejection.

In light of the amendments to the Specification, Claims, and the Remarks contained herewith, it is believed that the present application is in a condition for allowance. Should the Examiner deem that a personal or telephonic interview would be helpful in advancing this application toward allowance, she is encouraged to contact Applicants' undersigned representative at the below-listed telephone number.

Applicants file concurrently herewith a request for extension of time under 37 CFR § 1.136, with the appropriate fee under 37 CFR § 1.17. Should there exist a variance between that which is paid and owed, the Office is authorized to charge deposit account number 15-0030, in order to maintain pendency of the above-identified application.

Respectfully submitted,

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A handwritten signature in cursive script, reading "Daniel R. Evans", is written over a horizontal line.

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